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EDITORIAL

Does the spatial distribution of atrial arrhythmogenic substrate matter? Insights from the DECAAF II trial

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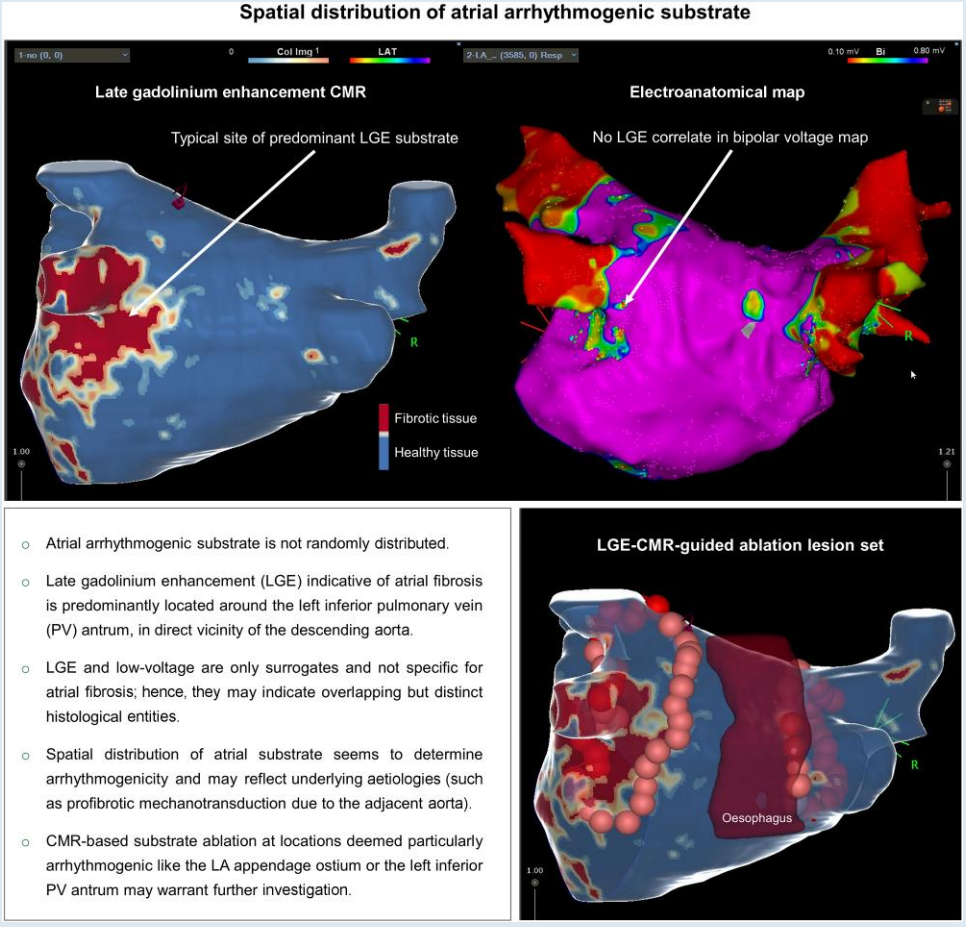
Graphical Abstract



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Fibrotic remodelling is considered the hallmark of arrhythmogenic substrate promoting atrial fibrillation (AF), and atrial fibrosis as detected by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is a key determinant of AF recurrences after pulmonary vein isolation (PVI).[1–5] In fact, the individual extent of left atrial (LA) LGE has been proposed to guide therapeutic decision-making, patient selection for PVI, and ablation strategies beyond PVI, respectively, albeit large randomized trials failed to prove benefit from LGE-CMR-guided ablation of fibrotic substrate.[1,3,6,7]

Fibrotic substrate is not randomly distributed

Meanwhile, it is well established that atrial arrhythmogenic substrate is not randomly distributed. In fact, previous CMR studies have consistently shown that in AF patients LGE is predominantly located posteriorly in the area surrounding the left inferior pulmonary vein antrum. In their post-hoc analysis of the DECAAF II trial in this issue of *Europace*, Assaf et al. provide yet another piece of evidence supporting this observation.[7–12] Typically, this predilection site is characterized by its direct vicinity to the descending aorta, suggesting a causal relationship—possibly through work of mechanical forces at the interface of the descending aorta and the LA wall. Indeed, it was recently demonstrated independently by us and Hopmann et al. that the extent of LGE indicating fibrosis in this area is determined by the proximity of the descending aorta, thus corroborating such concept of profibrotic mechanotransduction.[9,11]

Late gadolinium enhancement vs. low-voltage

Of note, studies using bipolar low-voltage determined through endocardial mapping as a surrogate are less consistent regarding the spatial distribution of arrhythmogenic substrate. While some studies encountered low-voltage areas primarily in the aforementioned peri-antral area of the left inferior pulmonary vein too, most of them reported low-voltage to be predominantly located at the LA anterior wall.[13,14] These seemingly conflictive observations with the different methods highlight the fact that, besides distinct methodological limitations of LGE-CMR and bipolar endocardial mapping in sensitivity and specificity, neither LGE nor endocardial low-voltage is specific for atrial fibrosis but should rather be considered surrogates that may indicate overlapping but different histological entities. To date, head-to-head comparisons based on a systematic histological validation of both atrial LGE and endocardial low-voltage are lacking.[15] However, both surrogates of arrhythmogenic substrate have proven to be predictive of AF recurrences after PVI.[1–3,16–19]

The spatial distribution of substrate has an impact on arrhythmogenicity

Interestingly, there is accumulating evidence that the individual distribution of arrhythmogenic substrate, rather than its mere presence or extent, can determine arrhythmia risk and may reflect underlying aetiologies and mechanisms.[9,12] In fact, we found the local LGE extent in the aforementioned peri-antral area of the left inferior pulmonary vein, where LGE is predominantly located, to best predict AF recurrence after PVI.[9] Against this background, it is noteworthy that, in their post-hoc analysis of the DECAAF II trial, Assaf et al. found only the regional LGE extent around the left atrial appendage (LAA) ostium to be predictive of arrhythmia recurrence, but unlike previous studies (including the predecessor DECAAF I and other trials), not the global extent of LA LGE nor the regional LGE around the left inferior pulmonary vein antrum.[1,3,9] These findings by Assaf et al. raise the question whether fibrotic substrate in the area surrounding the LAA ostium is particularly arrhythmogenic and whether risk stratification should be based on regional measurements rather than global LA LGE. While these findings are in partial conflict with previous data and certainly need confirmation, it has to be acknowledged that prior studies systematically excluded the LAA from their regional analyses and did not consider the LAA ostium as an individual segment either. While Assaf et al. excluded the LAA from analysis as well, the LAA ostium was defined as an individual segment. Of course, the actual LAA ostium itself would implicate only a small area that may not reach a critical arrhythmogenic mass for AF. However, based on the disclosed mean regional surface areas, it has to be assumed that the LAA ostium segment defined by Assaf et al. comprises a considerable portion (13%) of the LA surface area.

Why is the left atrial appendage ostial late gadolinium enhancement of predictive value only in the cardiac magnetic resonance–guided ablation group?

As mentioned above, the data of Assaf et al. are derived from the DECAAF II trial that randomized patients with persistent AF to receive either PVI plus ablation of fibrotic substrate as determined by LGE-CMR or PVI alone.[7] Interestingly, when stratifying this data according to study groups, it became apparent that only in the CMR-guided fibrosis ablation group the LGE around the LAA ostium was predictive of AF recurrence. This could potentially raise doubts about the general applicability of the data. While there is no obvious reason to explain the differences between the treatment groups, one could hypothesize that an incomplete ablation of the targeted substrate in patients in whom LGE was located around the LAA ostium could have had an impact. Of note, the atrial wall in this area, although outside the actual LAA, may contain extra-appendicular pectinate muscle with extremely thin tissue between the muscular trabeculae, and the operators might have ablated peri-LAA substrate more reluctantly not reaching homogenous transmural lesions.[20] Moreover, complete isolation of the LAA was not envisaged in the study protocol and would have implicated further considerations such as LAA closure. Taken together, although we can only speculate, reluctant, incomplete ablation resulting in iatrogenic substrate may have caused an unfavourable outcome in patients in whom peri-LAA fibrosis was targeted.

The left atrial appendage regional substrate and its potential arrhythmogenicity

Extrapolating their findings from the analysed region around the LAA ostium to the LAA itself, the authors raise interesting thoughts about the mechanistic role of LAA fibrotic substrate in AF, as well as its prognostic impact and predictive value. Indeed, evidence supporting LAA electrical isolation in selected patients is accumulating, and one could speculate that LGE in the LAA ostial area may be a surrogate for further arrhythmogenic substrate in the LAA itself.[21] Thus, although not substantiated by the data from Assaf et al., as the LAA has actually been excluded from analysis, such considerations are quite intriguing.[7] While enhanced automaticity has been proposed as the prevalent

mechanism of LAA-related arrhythmogenesis, further research on fibrotic arrhythmogenic LAA substrate may be warranted.[22] Unfortunately, the LAA itself is not well amenable to substrate analysis, neither by LGE-CMR nor through bipolar voltage mapping. In fact, the case of the LAA unveils the inherent limitations of both methods: On the one hand, atrial wall thicknesses down to 1 mm are already at the resolution limit of magnetic resonance. Indeed, the LAA wall, particularly between the trabeculae of pectinate muscle, can be even thinner, rendering valid LGE analysis challenging, if not impossible.[20] On the other hand, with LAA bipolar signal amplitudes more than two-fold above the LA average, the established thresholds for low-voltage substrate validated for the LA are not applicable to the LAA.[23] However, previous studies have reported on arrhythmogenic LAA substrate in terms of slow conduction, which may be a more suitable surrogate and an avenue for future research.[24] Of note, a recent international collaborative effort has identified the base of the LAA as one of the LA sites where atrial electrograms display decremental properties most frequently, thus supporting the finding of Assaf et al.[25]

Conclusion

This post-hoc analysis of the DECAAF II trial highlights the significance of spatial substrate distribution in AF. In fact, regional substrate analyses may yield higher predictive value compared with global analyses that do not take spatial distribution into account. It is this kind of post-hoc analysis that underscores the immense value that can be derived from large, well-designed, and well-executed randomized trials like DECAAF II. Having said that, the DECAAF II investigators are to be commended once more for their effort and for providing invaluable insights into the role of arrhythmogenic substrate and its therapeutic implications in AF.

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